An Introduction to Environmental Pharmacology

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Chapter 1

PharmEcovigilance
Aligning Pharmacovigilance with Environmental Protection

Christian G Daughton & Ilene S Ruhoy

Traditionally, the focus of pharmacovigilance has been directed at detecting, monitoring, collecting, assessing, and evaluating data regarding the human hazards posed by medicines, with the primary objective to reduce or prevent future harm to patients and other end users. As such, the primary focus has been on adverse effects as compiled by various organizations and government agencies after a medication has come into commercial use — post-marketing analysis; one example is MedWatch, FDA's Adverse Event Reporting Program (http://www.fda.gov/medwatch/how.htm). Safety, as represented by the types and incidence of adverse drug reactions (ADRs), is an aspect of pharmacology that has garnered increasing attention, as witnessed by a series of widely publicized drug recalls, label revisions, and withdrawals over the last few years in the U.S. Although the traditional role of pharmacovigilance is well defined, one aspect has been poorly developed. In contrast with adverse, intolerable, or undesired effects, a much less developed aspect of pharmacovigilance is tracking the failure of a medication to perform (lack of a desired effect) — failure to achieve the effect or outcome for which the drug was designed, but in the absence of untoward effects. Monitoring both ends of the spectrum of outcomes from drug administration is important — adverse reactions as well as ineffectiveness.

While the role of pharmacovigilance has long focused on the occurrence of adverse outcomes from the intended use of pharmaceuticals in both humans and domestic animals, another responsibility has only more recently emerged — the need to also protect the environment from unintentional contact with the active ingredients in pharmaceuticals. Here, we provide an overview to this new dimension of pharmacovigilance, capturing its expanded role in environmental protection with the term "pharmEcovigilance."

PharmEcovigilance can employ a wide spectrum of means to minimize the ecological footprint of medications as well as the possibility of their causing harm to humans and domestic animals not just by way of intended use, but also by their unintended use as well as cessation of use.

Pharmaceuticals as Environmental Pollutants

It is only natural that attention has been historically directed at maintaining the health and safety of the populations for which medications have been developed — humans as well as domestic animals. But many drugs lead double lives. Once the active pharmaceutical ingredients (APIs) in administered medications have completed their intended purposes (in therapy, disease prevention, diagnosis, or cosmetic/lifestyle alteration), they can take on renewed lives in the environment. APIs from a large and diverse spectrum of pharmaceuticals can enter the environment as trace contaminants, especially in waters, at individual concentrations generally less than a part per billion (µg/L), but sometimes more. These trace residues may pose risks for aquatic life (Boxall *et al.* 2004; Cleuvers 2003; Daughton and Ternes 1999; Jones et al. 2002; Kidd *et al.* 2007) and cause concern with regard to human exposure, such as with contaminated drinking water supplies or food sources (Daughton 2004, 2008).

The predominate route by which APIs gain entry to the environment is via the discharge of raw and treated sewage contaminated with APIs simply as a result of medications used for the purposes for which they were designed. Residues of APIs from drugs that are administered parenterally (e.g., via injection/infusion) and enterally (e.g., via ingestion) are often excreted in feces and urine, and topically applied medications can be washed from skin during bathing. For most APIs, the fraction of unchanged, parent API transferred to the environment is attenuated as a result of metabolic alteration in the body or transformation within a sewage treatment facility (such as by microbial degradation). For some APIs, only a small percentage of the total amount used is ever transported to the environment. For others, this percentage can approach 100%.

A secondary route of transfer of APIs to the environment is from the purposeful, direct disposal of leftover or unwanted medications to sewers and trash (see chapter 4 of the same authors). The relative significance of disposal with respect to excretion and bathing, however, is poorly understood and has long been the topic of some debate.

Pharmacovigilance and Environmental Protection

With the double lives of APIs in mind, a major potential aspect of pharmacovigilance that had been ignored up until recently (e.g., Kummerer and Velo, 2006; Rahman and Khan 2006; Rahman *et al.* 2007) is the role it could play in protecting the environment. Pharmacovigilance and environmental protection are intimately tied — just as are human health and ecological integrity (Daughton 2003a). There are two major dimensions to their interrelationship. The first addresses ecological effects. The study and monitoring of ADRs can potentially provide information valuable for informing the types of effects that drug contaminants in the environment might possibly have on non-target organisms, especially aquatic organisms. The second addresses ecological exposure. The study of the numerous factors that are and could be scrutinized with the proper application of pharmacovigilance could provide valuable insights into the many ways in which the introduction of drugs to the environment might be minimized or reduced. This would not only reduce ecological exposure to drug contaminants, it would also reduce the possibility of these residues (albeit very low levels) making their way into our food and drinking water supplies, thereby further reducing human exposure.

PharmEcovigilance: Expanding the Scope of Pharmacovigilance

A holistic approach to pharmacovigilance would encompass all of the many aspects of the drug distribution/consumption chain and identify those areas where changes could lead to reduced release of APIs to the environment. In the process, human safety could be improved as well, such as by reducing the stockpiling of leftover or unwanted drugs, which can lead to human poisonings (Ruhoy and Daughton 2007). Several terms have appeared in the literature to describe such a holistic approach, including: ***Environmental***

Pharmacology, Ecopharmacology & Pharmacoenvironmentology (Kummerer and Velo, 2006; Rahman and Khan 2006; Rahman et al. 2007). While one of the last things that science needs is yet more jargon, a term more similar to that of pharmacovigilance but one that instantly conveys its linkage with the environment would better serve to draw attention to the need for expanding its scope. With this said, changing but one letter provides the instantly recognizable term "PharmEcovigilance," which can be pronounced in a way similar to pharmacovigilance — with the primary accent on the first syllable.

The conceptual framework long used by the U.S. EPA for assessing and managing environmental risks follows a natural progression of events beginning with the sources of release of chemicals to the environment followed by the events (e.g., transport and transformation) leading to biological exposure, followed by the possibility for biological effects, and, ultimately, altered function or disruption of homeostasis (e.g., disease). This framework (shown as part of Figure 1) can be used to highlight the role that pharmacovigilance has traditionally played (Figure 1, dashed line on right side), which is restricted to the domains of pharmacology, toxicology, and epidemiology. Expansion of this role to also account for the earlier environmental events in the environmental risk framework (Figure 1, dotted lines at top) illustrates the more holistic approach that would define pharmEcovigilance. Although several terms (cited above) have been used in the literature to try and capture the need for expanding the role of pharmacovigilance to accommodate the environmental impact of the practice of medicine, none has ever been accompanied by a conceptual framework. We hope that Figure 1 will catalyze productive discussions in this regard.

A wide range of factors modulate the consumption of medications. These factors can increase or reduce the quantities and types of medications consumed; most apply to human medications, but many of the same principles apply also to veterinary drugs. Consumption, or lack of consumption, affects the types and quantities of APIs that can be eventually released to the environment by two major pathways. The first route stems from the intended use of the medication — by excretion of feces and urine containing unaltered APIs from enteral and parenteral drugs (and transdermal drugs), or by dissolving or dislodging APIs from dermally applied drugs during bathing; this route also releases metabolites and can lead to further degradation products. The second route is direct discarding of leftover, unwanted (e.g., expired) medications into trash or septic drains/toilets. Except for disposal to trash, both routes feed into sewage or septic systems from where those undegraded APIs in the aqueous phase can then enter groundwaters and surface waters; those remaining in the sludge can be inadvertently transferred to land by the use of processed biosolids for soil amendments or fertilizer.

These use-modulating factors can be arrayed (see Table 1) among seven general categories: Promotionals (Pharmaceutical sales representatives and Manufacturers /Distributors), Counteracting Promotionals (programs that attempt to counter-balance promotionals), Prescribing, Dispensing, Consumer Involvement/Behavior, and Non-adherence/Non-compliance. Each factor can lead to either increasing or decreasing consumption of drugs by affecting one or more of five aspects of the drug-distribution and consumption chain: Prescribing, Dispensing, Purchasing, Accessibility, and Direct Wastage (leftover, unused drugs); although most of the factors can affect more than one of these categories, only the primary affected category is usually indicated in Table 1. Approaches for improving the performance of many of these factors were first summarized in a 2-part monograph on the concept of the "green pharmacy" (Daughton 2003a,b); other ideas have since appeared, such as drug labels with ratings relevant to various ecological criteria (e.g., Wennmalm and Gunnarsson, 2005).

Controlled improvements in the ways in which the numerous factors listed in Table 1 are designed or implemented could significantly reduce ADRs (the right side of Figure 1) as well as reduce the release of APIs to the environment (the left side of Figure 1). It should also be said that while the benefits are clear for the removal from the market of high-risk medications, continued usage of ineffective drugs is not also without consequence. Ineffective drugs can obscure the need for better treatment. But further, although they may have no unfavorable effects in humans, they serve as a source of chemicals with largely unknown potential for effects in the environment. Therapeutically ineffective medications play roles as sources of APIs in the environment by both excretion and disposal since physicians will often prescribe new treatment regimens when the desired therapeutic effect is not achieved. This, in turn, leads to the accumulation and eventual disposal of the unused portion of the original prescribed quantity.

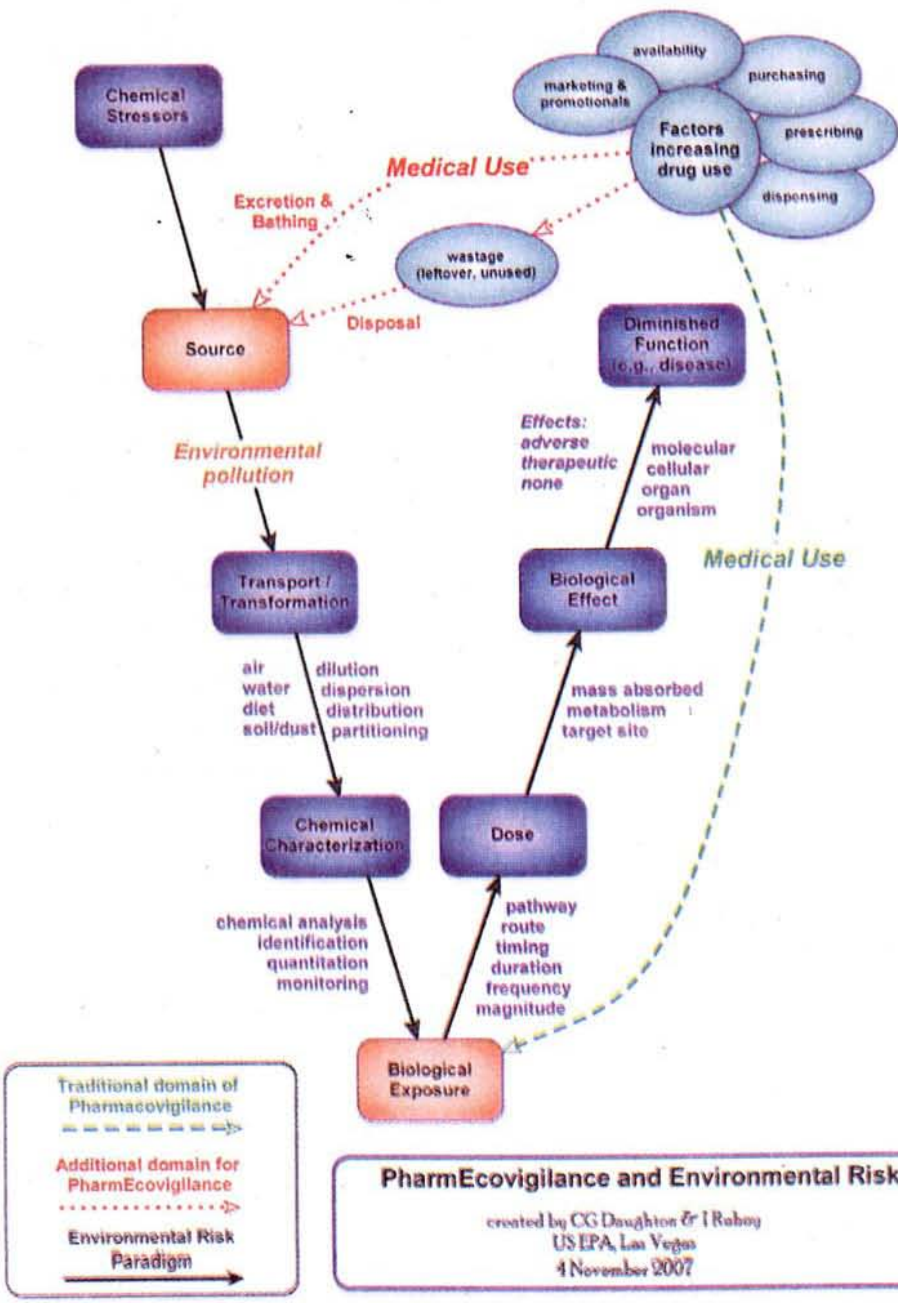

Figure 1. PharmEcovigilance and the Environmental Risk Paradigm

Table 1. Factors that modulate consumption of medications, ultimately affecting introduction of APIs to the environment after intended usage (via excretion or bathing) or from disposal of unwanted leftovers.

	Modulation of Drug Consumption via :				
Leading to: / Factor	Prescribing	Dispensing	Purchasing	Accessibility	Direct Wastages; leftover, unused
Promotionals: Pharmaceuticals Sales representatives	Ready availability of free medications (samples). Short trials can minimize wastage, but can also lead to wastage by the patient, and accumulation of expired drugs by physician. Detailing can promote over-prescribing.				
Detailing (sales calls to physicians)	▲ ↑				
Sampling				▲	▲▼↓
Promotionals: Manufacturers/ Distributors	Physician education sponsored by manufactures poses possible conflicts of interest and the possibility of promoting less-efficacious medications. Virtual sampling facilitates free medications.				
Educational meetings & events for physicians	▲				
CME linked to marketing	▲				
Medical journal advertising	▲				
E-Sampling		▲			▲
E-Vouchers		▲			▲
Virtual detailing	▲				
Counteracting Promotionals	Physician and consumer education centered around evidence-based medicine can promote reduced consumption. Insurance-restricted formularies and P4P can reduce prescribing. Drug-abuse prevention programs reduce consumption of controlled and illegal substances.				
Educational counter-detailing ("academic-detailing") [checks and balances counter approach to balance drug representative detailing]	▼				▼
Point-of-care dispensing	▼▲			▲	
Physician education	▼				
Evidence-based medicine	▼				
Restrictive formularies	▼				
P4P: Pay for performance	▼				
Consumer education	▼				▼
Abuse and Addiction Prevention				▼	▼

Cont.

Prescribing	Confusing instructions, frequent changes in scripts, polypharmacy, patient demands can all lead to patient non-compliance and accumulation of unused drugs.Personalized medicine can promote compliance. Drugs to counteract ADRs lead to polypharmacy and non-compliance.				
Drugs prescribed based on patient requests	▲				
Drugs prescribed as "pm" (use as needed)					▲
Extra-label (off-label) prescribing	▲				
Changes in treatment (therapy switches)	▲				
Drugs with complicated instruction					▲
Drugs prescribed to treat side effects (e.g. Polypharmacy)	▲				
Lack of physician knowledge (e.g. imprudent prescribing: non-evidence-based)	▲				▲
Over-prescribing	▲				▲
Personalized reduced doses	▲				▼
Drug Utilization Review (DUR), physician profiling (outside review of prescribing practices by insurers and others)					▼
Dispensing	Insurance efforts to promote cost-savings via multi-month supplies of medications, free/low-cost pharmacy pricing for certain drugs, and efforts to expand availability of behind-the-counter medications and expand the authority of pharmacists to prescribe can all promote over-comsumption. Non-standard labeling leads to consumer confusion and medication error. Trial scripts and DUR (or "physician profiling" against accepted norms) can reduce leftovers.				
Extended and mandated quantities (insurance requirements for 30 to 90-days supplies)		▲			
Free/low cost medications		▲	▲	▲	▲
Expanded BTC avialabiltiy (behind-the-counter)		▲	▲	▲	
Non-standardized prescription medication labels					▲
Small-quantity trials					▼
Installment dispensing					▼
Prescribing Pharmacists (point-of-care prescribing)		▲			▲
Dispensing Physicians		▲			▲

Cont.

Consumer Involvement/Behavior	Low-cost and unknown-quality medications, incorrect information, prescription drugs approved for over-the-counter sales, use of multiple doctors can all lead to excessive purchasing.				
Purchase of excessive quantities of OTC drugs (losses due to expiry)			▲		▲
Internet patient forums (sharing misinformation)	▲				
Internet and gray-market availability			▲	▲	▲
Responding to DTC (direct-to-consumer) advertising	▲				
Rx-to-OTC (non-legend drugs) switches			▲	▲	▲
Marketing of human drugs fo pets	▲				▼
Doctor shoping	▲				▲
Non-adherence/Non-compliance	Patient non-compliance is a major factor in failure to consume full-courses of medications. Failure to perceive progress or status of treatment, and failure to understand directions lead to leftovers.				
Ineffectiveness					▲
ADRs: Adverse drug reactions					▲
Drugs with complicated delivery systems or labels					▲
Complicated treatment regimes					▲
Patient confusion (e.g. illiteracy, complicated/ non-standarized labels)					▲
Diminished incentive to continue therapy (e.g. perceived lack of benefit)					▲
Death of patient (leftover medications)					▲
Abandoned or lost drugs (including recalled drugs)					▲
Inaccessible, irretrievable liquid residues remaining in used vials, syringes, dispensers and other containers					▲
Disease state (dementia, depression, etc.)					▲
Poor perception of disease severity (e.g. symptoms no longer evident; percevied improvement)					▲
Stock pilling (e.g., boarding) for future use (leads to expiration)					▲
Inappropriate & unusable charitable contributions					▲
Drug sharing				▲	▼

Footnotes : ↑Upward facing triangle (red ▲) indicates that factor tends to INCREASE consumption or wastage via one or more routes.

↓ Downward facing triangle (blue ▼) indicates that factor tends to REDUCE consumption or wastage via one or more routes

Connections between Human and Ecological Health

The occurrence of API residues in the environment (especially in drinking water) makes obvious the connection that exists between the practice of medicine and the protection of the condition of the environment. The two are intimately tied but little recognized as such. The two share many commonalities and connections. Consider the processes of data collection, articulation of symptomology, epidemiology, diagnosis, mitigation/treatment, prognosis, determination of vulnerability, and pollution/disease prevention. Each of these plays a critical role in both healthcare and environmental protection — in the "ecology of health" and in the "health of ecology." Improvements in one can impart collateral, unanticipated improvements in the other.

With a new, added focus on environmental protection, active programs in pharmEcovigilance could play the premier role in pollution reduction or pollution prevention with respect to the release of APIs into the environment. By optimizing the consumption and usage of medications to achieve the best healthcare outcomes for consumers, nearly all of the sources of easily controlled, environmental release of APIs could be best managed. Although pharmacovigilance currently follows postmarket events for humans (and domestic animals), analogous events' concerning the environment have been largely ignored. With no system in place to routinely detect and report abnormal effects in the environment, this gap would be filled by expanding the traditional domain of pharmacovigilance.

Wastage of Medications Necessitates Disposal

One of the primary aspects of drug consumption is that many medications remain unused once they are purchased. Numerous factors lead to the accumulation of leftover, unused medications (Daughton 2007; Ruhoy and Daughton 2007; Ruhoy and Daughton, in preparation). Leftover drugs eventually necessitate disposal, a very complicated issue in the U.S. (Daughton 2007). A controversial aspect of drug disposal is how significant it might be as a contributor to the overall types and levels of API residues that occur in the environment. It is unclear what portions of API residues in the environment originate from drug disposal, and research to determine the significance of disposal is just beginning (Ruhoy and Daughton 2007). While well-designed, efficient programs to collect unused drugs from consumer and other end users for proper disposal (e.g., via incineration or hazardous waste landfill) would certainly be welcome, these are but interim, stop-gap measures that are not economically sustainable. **With pharmEcovigilance, an ultimate objective should be the design and implementation of changes in the many aspects of the drug distribution/consumption chain in order to minimize or eliminate the generation of leftover medications — so that disposal is not needed to begin with.**

Beyond the proper disposal of unwanted drugs, the ultimate focus with regard to pollution prevention could be in the way in which drugs are prescribed and dispensed. Guided by pharmEcovigilance, the healthcare system could be re-designed so that only the most efficacious medications are prescribed in minimal doses, individualized for each patient, and dispensed in quantities and for durations to ensure their full consumption. The ideal outcome would be the absence of leftover drugs requiring disposal. Redesign of prescribing and dispensing practices would also reduce the quantities of APIs that gain entry to the environment (via excretion and bathing) as a result of their intended use (assuming that doses are reduced, such as by better-targeted delivery systems). When clinically appropriate, one drug could be prescribed in preference to another that may have a less favorable environmental fate profile (e.g., Wennmalm and Gunnarsson, 2005). Many additional factors beyond those involved with prescribing and dispensing play roles and should also command attention. Most of these factors are summarized in Table 1. The end result of a "greener" healthcare system would be not just a cleaner environment, but also more efficient utilization of healthcare resources, reduced healthcare costs, improved healthcare outcomes, and reduced incidence of purposeful abuse and accidental poisonings from diversion of stockpiled drugs. The health of humans and the environment is indeed intertwined — steps to protect one protect the other.

Unintended, Unwelcome Exposure

One final note: The obvious argument against taking ecological concerns into account during prescribing (or during consumer purchase of OTC drugs) is that the benefits to the patient should outweigh considerations of risk to the environment. But a problem inherent with this stance is that included in possible ecological risks are the unknowns associated with possible future unwelcome exposure of non-patients — those for whom the medication was never intended (and perhaps might even be contraindicated) and who would ordinarily desire to never be exposed to the medication (Daughton 2008). By not factoring in ecological exposure, the risk-benefit equation is incomplete. While the risks incurred by the target organism (human or domestic animal undergoing therapy or prophylaxis) are largely known (and adverse event reporting can further reduce the uncertainty), the risks for non-target organisms (including unintentional human exposure via contaminated drinking water and food) are largely unknown, particularly because exposure can be chronic, long-term, and involve multiple APIs in combination together.

Conclusion

Wherever we live or travel, we impart unique chemical signatures on the environment in the form of minute residues of pharmaceuticals and personal care products that we excrete, wash from our bodies, or discard to sewerage or trash. While the contributions from each individual may be insignificant by themselves, the combined contributions from all individuals, as well as from medicated animals, reach measurable levels in surface and ground waters and on land receiving treated sewage (Daughton and Ruhoy, 2007).

Such is the importance of pharmEcovigilance. Its ultimate objective should be on ensuring that the life-cycle of pharmaceuticals is one that is sustainable. The ideal manifestation of this would be the elimination of drug waste, an achievement that holds great potential for the collateral improvement in health care with improved therapeutic outcomes, reduced costs, and lessened possibility of drug abuse and poisonings. Since human and ecological health are intimately linked, efforts to improve one will inevitably lead to improvements in the other.

Notice:

The views expressed in these Proceedings are those of the individual authors and do not necessarily reflect the views and policies of the United States Environmental Protection Agency. Scientists in EPA have prepared the EPA sections, and those sections have been reviewed in accordance with EPA's peer and administrative review policies and approved for presentation and publication.

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